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Johji Inazawa

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER

BOESEN, CHRISTIAN C

ART UNIT

PAPER NUMBER

1639

NOTIFICATION DATE

DELIVERY MODE

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ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/589,347	Applicant(s) INAZAWA ET AL.	
	Examiner CHRISTIAN BOESEN	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 August 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) 9-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 August 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>04/09/2008 and 01/16/2009</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

This Non-Final Office Action is responsive to the communication received 08/13/2009.

Election/Restrictions

Applicant's election without traverse in the reply filed on 08/13/2009 of group I, claims 1-8 is acknowledged. Applicant has elected the following species: A. the CGH method (claims 3-4); B. ABCB1 gene (claim 6). The restriction is deemed proper and is made FINAL.

Claims 1-12 are pending.

Claims 9-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election was made **without** traverse in the reply filed on 08/13/2009.

Claims 1-8 are under examination in this Office Action.

Priority

This application is filed under 35 U.S.C 371 of PCT/JP04/01574 (filed on 02/13/2004).

Information Disclosure Statement

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The information disclosure statements (IDS) submitted on 04/09/2008 and 01/16/2009 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner.

Claim Objections

A. **Claim 1** is objected to because of the following informalities: The claim recites the acronym “ABC” in line 3 of claim 1. Applicant is required to add "ATP binding cassette (ABC)" in place of the first use of "ABC".

Claim 3 is objected to because of the following informalities: The claim recites the acronym “CGH” in line 2 of claim 3. Applicant is required to add "comparative genome hybridization (CGH)" in place of the first use of "CGH".

B. **Claim 3** is objected to because of the following informalities: The claim recites “nethod” in line 1 of claim 3. Applicant is required to correct the typographical/grammatical error.

Claim 7 is objected to because of the following informalities: The claim recites “... as in index.” in line 7 of claim 7. Applicant is required to correct the typographical/grammatical error.

Claim 8 is objected to because of the following informalities: The claim recites “substrte” in line 2 of claim 8. Applicant is required to correct the typographical/grammatical error.

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Claim 8 is objected to because of the following informalities: The claim is missing "the" where the claim recites "wherein" the "DNA fixed on said" on line 2 of claim 8. Applicant is required to correct the typographical/grammatical error.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. **Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the limitation "the CGH method, the flow cytometry method, the ELISA method, the DNA chip method, or the quantitative PCR method" in line 2 of claim 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 4 recites the limitation "the CGH method or the DNA chip method" in line 2 of claim 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 7 recites the limitation "the DNA of a test cancer cell" in line 2 of claim 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 7 recites the limitation "said DNA-fixed substrate" in line 4 of claim 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 7 recites the limitation "the test DNA" in line 6 of claim 7. There is insufficient antecedent basis for this limitation in the claim.

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B. Claim 1 is indefinite and unclear in their recitation for being incomplete by omitting essential steps or ingredients, such omission amounting to a gap between the steps. See MPEP § 2172.01.

For example, there appears insufficient steps and ingredients to carry out the methods of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs. There is no nexus between the preamble of the claim (detecting drug resistance) and the one active method step (detecting amplification).

C. Claim 7 is indefinite and unclear in the recitation of “the fluorescent dye obtained as a result of the hybridization as in index.” Is the fluorescent dye “obtained as a result”, or is the detection “obtained as a result”?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

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the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts (11/2001 The Journal of Pharmacology and Experimental Therapeutics volume 299 page 434) in combination with Efferth (03/2001 Current Molecular Medicine volume 1 page 45) in further view of Wessendorf (01/2002 Laboratory Investigation volume 82 page 47).

Claims are drawn to A detection method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs, which comprises detecting amplification of one or more types of genes selected from ABC transporter genes and BCL2 family genes consisting of ABCA3 gene, ABCB6 gene, ABCB10 gene, ABCC4 gene, ABCC9 gene, ABCD3 gene, ABCD4 gene, ABCE1 gene, ABCF2 gene, BCL2L2, BCL2L10, BCL2L1, and BCLZAI, in said test cancer cell.

Regarding **claim 1**, Watts teaches detecting acquisition of the **drug resistance** of a test cancer cell to anticancer drugs by **detecting amplification of ABC transporter genes** in a test **cancer cell**, for example, Figure 1, Figure 2, Figure 3a, and

"In the human multiple **myeloma cell** line, RPMI 8226, doxorubicin selection at 60 nM resulted in a resistant variant, 8226/Dox6. Further selection of 8226/Dox6 with 400 nM doxorubicin led to the highly resistant 8226/Dox40 cell line. Both 8226/Dox cell lines possess a **multidrug-resistant** phenotype." (page 434 left bottom) and "we have analyzed the RPMI 8226 cell line and its **multidrug-resistant** variants, 8226/ Dox6 and 8226/Dox40, using 5760-element cDNA microarrays to identify differential gene expression." (page 435 left bottom) and " the **MDR1 gene** was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in a all replicates (Fig. 1)." (page 436 right center) and "Figure 3a shows a progressive

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increase in **MDR1 mRNA expression** from none in RPMI 8226 to an intermediate level in 8226/Dox6 and finally **a high level of expression** in 8226/Dox40." (page 436 right bottom).

MDR1 is another name for the ABCB1 gene.

Regarding **claim 2**, Watts teaches amplification of the ABCB1 gene is an index of acquisition of drug resistance to doxorubicin, for example, Figure 1, Figure 2, Figure 3a, and

"In the human multiple myeloma cell line, RPMI 8226, doxorubicin selection at 60 nM resulted in a resistant variant, 8226/Dox6. Further selection of 8226/Dox6 with 400 nM doxorubicin led to the highly resistant 8226/Dox40 cell line. Both 8226/Dox cell lines possess a multidrug-resistant phenotype." (page 434 left bottom) and "we have analyzed the RPMI 8226 cell line and its multidrug-resistant variants, 8226/ Dox6 and 8226/Dox40, using 5760-element cDNA microarrays to identify differential gene expression." (page 435 left bottom) and " the MDR1 gene was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in a all replicates (Fig. 1)." (page 436 right center) and "Figure 3a shows a progressive increase in **MDR1 mRNA expression** from none in RPMI 8226 to an intermediate level in 8226/Dox6 and finally **a high level of expression** in 8226/Dox40." (page 436 right bottom).

Regarding **claim 3**, Watts teaches detection is carried out by the **DNA chip** method, for example, Figure 1 and

"we have analyzed the RPMI 8226 cell line and its multidrug-resistant variants, 8226/ Dox6 and 8226/Dox40, using 5760-element **cDNA microarrays** to identify differential gene expression." (page 435 left bottom) and " the MDR1 gene was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in a all replicates (Fig. 1)." (page 436 right center).

Regarding **claim 4**, Watts teaches detection is carried out by the **DNA chip** method, for example, Figure 1 and

"we have analyzed the RPMI 8226 cell line and its multidrug-resistant variants, 8226/ Dox6 and 8226/Dox40, using 5760-element **cDNA microarrays** to identify differential gene expression." (page 435 left bottom) and " the MDR1 gene was identified as differentially

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expressed between RPMI 8226 and the 8226/Dox cell lines in all replicates (Fig. 1)." (page 436 right center).

Regarding **claim 5**, Watts teaches a substrate used in the **DNA chip** method is a DNA fixed substrate wherein the DNA comprises one or more types of genes selected from **ABC transporter genes**, for example, Figure 1, Figure 2, Figure 3a, and

"we have analyzed the RPMI 8226 cell line and its multidrug-resistant variants, 8226/Dox6 and 8226/Dox40, using 5760-element **cDNA microarrays** to identify differential gene expression." (page 435 left bottom) and "the **MDR1 gene** was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in all replicates (Fig. 1)." (page 436 right center) and "Figure 3a shows a progressive increase in **MDR1 mRNA expression** from none in RPMI 8226 to an intermediate level in 8226/Dox6 and finally a high level of expression in 8226/Dox40." (page 436 right bottom).

MDR1 is another name for the ABCB1 gene.

Regarding **claim 6**, Watts teaches a substrate used in the **DNA chip** method is a DNA fixed substrate wherein the DNA comprises one or more types of genes selected from **ABC transporter genes** consisting of **ABCB1**, for example, Figure 1, Figure 2, Figure 3a, and

"we have analyzed the RPMI 8226 cell line and its multidrug-resistant variants, 8226/Dox6 and 8226/Dox40, using 5760-element **cDNA microarrays** to identify differential gene expression." (page 435 left bottom) and "the **MDR1 gene** was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in all replicates (Fig. 1)." (page 436 right center) and "Figure 3a shows a progressive increase in **MDR1 mRNA expression** from none in RPMI 8226 to an intermediate level in 8226/Dox6 and finally a high level of expression in 8226/Dox40." (page 436 right bottom).

MDR1 is another name for the ABCB1 gene.

Regarding **claim 7**, Watts teaches allowing **control DNAs** and the DNA of a test cancer cell used as a target of detection of acquisition of **drug resistance**, each of which was **labeled**

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with each different fluorescent dye, to simultaneously contact with said **DNA-fixed substrate**, so as to conduct hybridization; and quantitatively **detecting amplification or deletion** of a specific region of the test DNA by using the fluorescent dye obtained as a result of the **hybridization as an index**, for example, Figure 1, and

"In the human multiple myeloma cell line, **RPMI 8226**, doxorubicin selection at 60 nM resulted in a resistant variant, 8226/Dox6. Further selection of 8226/Dox6 with 400 nM doxorubicin led to the highly resistant 8226/Dox40 cell line. Both 8226/Dox cell lines possess a **multidrug-resistant** phenotype." (page 434 left bottom) and "we have analyzed the RPMI 8226 cell line and its **multidrug-resistant** variants, 8226/ Dox6 and 8226/Dox40, using 5760-element **cDNA microarrays** to identify **differential gene expression**." (page 435 left bottom) and " the **MDR1 gene** was identified as differentially expressed between RPMI 8226 and the 8226/Dox cell lines in a all replicates (Fig. 1)." (page 436 right center) and "**Labeled cDNA** from two reactions (one **Cy3-labeled**, one **Cy5-labeled**) was combined and purified on a microcon-50 column using four buffer exchanges" (page 436 left top) and "Slides were scanned for **Cy3 and Cy5 fluorescence** using a Axon GenePix 4000 microarray reader (Axon Instruments, Foster City, CA) and **quantitated** using GenePix software. The RPMI 8226 versus 8226/Dox6 hybridizations were performed in triplicate, and the **RPMI 8226 versus 8226/Dox40 hybridizations** were performed seven times." (page 436 left top).

While Watts teaches a method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting amplification of ABC transporter genes in a test cancer cell, Watts does not teach the ABCA3 gene as recited in claims 1, 2, and 5 or etoposides as recited in claim 2 or genomic DNA as recited in claim 8.

Regarding **claim 1**, Efferth teaches a detection method of detecting acquisition of the **drug resistance of a test cancer cell to anticancer drugs**, which comprises detecting **amplification** of one or more types of genes selected from **ABC transporter genes** including the ABCA3 gene in said test cancer cell, for example,

"**ABCC1 (MRP1)** has been first identified in a multidrug-resistant, P-glycoprotein negative lung cancer cell line MRP1 acts as a drug-efflux pump **rendering cancer cells resistant to cytostatic drugs**.... Evidence for a causative contribution of MRP1 to drug

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resistance came from **transfection experiments**" (page 51 left center) and "MRP2 is involved in the **development of multidrug resistance** as well as in resistance to cisplatin or methotrexate resistance, both of which are not involved in the classical multidrug resistance phenotype" (page 51 right bottom) and "The ABCC3 (MRP3) gene is probably not responsible for the Dubin-Johnson syndrome, since MRP3 is expressed in the liver of Eisai hyperbilirubinemic rats and TR(-) mutant rats. It is involved in **anticancer drug resistance**" (page 52 left top) and "identified the ABCC6 (MRP6) gene in **epirubicin-resistant leukemia cells.**" (page 52 left center) and "Unraveling ABC transporter genes as responsible factors for resistance to cancer chemotherapy has opened new avenues for diagnosis of **drug-resistant tumors.**" (page 56 left bottom).

Regarding **claim 1**, Efferth teaches a detection method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs, which comprises detecting amplification of one or more types of genes selected from ABC transporter genes including the **ABCA3 gene** in said test cancer cell, for example, Table I and Table II.

Regarding **claim 2**, Efferth teaches a detection method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs, which comprises detecting amplification of one or more types of genes selected from ABC transporter genes including the **ABCA3 gene** in said test cancer cell, for example, Table I and Table II.

Regarding **claim 2**, Efferth teaches amplification of the ABCC1 (MRP1) gene is an index of acquisition of drug resistance to **etoposides**, for example,

"This indicates that MRP1 exports drugs out of the cell and sequesters drugs into vesicles. MRP1 knock-out mice are hypersensitive to **etoposide**, especially in bone marrow, testis, and kidney.... MRP1 has various functions: 1. transport of exogenous allocrites: a. anticancer drugs, i.e. doxorubicin, **etoposide**, or vincristine ...;" (page 51 left bottom).

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Regarding **claim 5**, Efferth teaches a detection method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs, which comprises detecting amplification of one or more types of genes selected from ABC transporter genes including the **ABCA3 gene** in said test cancer cell, for example, Table I and Table II.

While Watts and Efferth teach a method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting amplification of ABCA3 transporter gene in a test cancer cell, Watts and Efferth do not teach genomic DNA as recited in claim 8.

Regarding **claim 8**, Wessendorf teaches DNA fixed on said DNA-fixed substrate, test DNA, and control DNA are **genomic DNAs**, for example, Figure 2 and

"we investigated the potential of matrix-CGH using universally amplified **genomic DNA** from three tumor cell samples (see Fig. 2):" (page 49 left center).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to provide Watts's method of detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting amplification of ABC transporter genes in a test cancer cell in Efferth's method of detecting acquisition of the drug resistance of a test cancer cell to etoposides by detecting amplification of ABCA3 in a test cancer cell and in Wessendorf's method screening using genomic DNA **to arrive at applicant's invention with the above cited references before them.**

The present claims would have been obvious because the **substitution** of one known element the MDR1 gene, taught by Watts for another the ABCA3 gene, taught by Efferth would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting

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amplification of ABCA3 gene in a test cancer cell). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

The present claims would have been obvious because the **substitution** of one known element doxorubicin, taught by Watts for another etoposides, taught by Efferth would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. detecting acquisition of the drug resistance of a test cancer cell to etoposides by detecting amplification of ABC transporter genes in a test cancer cell). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

The present claims would have been obvious because the **substitution** of one known element cDNA, taught by Watts for another genomic DNA, taught by Wessendorf would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. detecting acquisition of the drug resistance of a test cancer cell to anticancer drugs by detecting amplification of genomic ABC transporter genes in a test cancer cell). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to CHRISTIAN BOESEN whose telephone number is 571-270-1321. The Examiner can normally be reached on Monday-Friday 9:00 AM to 5:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher S. Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christian Boesen/
Examiner, Art Unit 1639

/SUE LIU/
Primary Examiner, Art Unit 1639